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Detection of Sibutramine and Fluoxetine Adulteration in Unregistered Weight-Loss Supplement Products Containing Natural Extracts Sold in Four Provinces of Lao PDR

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Abstract

The adulteration of unregistered weight-loss supplements marketed as natural products with undisclosed pharmaceutical substances is a significant public health concern. Sibutramine is an anti-obesity drug and withdrawn from the market due to associated cardiovascular risks and fluoxetine, selective serotonin reuptake inhibitors are among the most commonly reported adulterants. Their undeclared presence, particularly when combined, poses serious risks to consumer health. This study aimed to determine the presence and quantity of sibutramine and fluoxetine in unregistered weight-loss supplements using a validated High-Performance Liquid Chromatography with Ultraviolet Detection (HPLC-UV) method. An HPLC-UV method for the determination of sibutramine and fluoxetine were developed and validated. A total of 100 samples of unregistered weight-loss supplements containing natural extracts were collected from markets and retail stores across four provinces of Lao PDR. Samples were analyzed by HPLC-UV at a detection wavelength of 224 nm. The method shown excellent linearity ($R^2 > 0.999$) in a concentration range of 5-100 µg/mL. Limits of detection were 0.18 µg/mL for sibutramine and 0.19 µg/mL for fluoxetine, while limits of quantification were 0.55 µg/mL and 0.59 µg/mL, respectively. Accuracy ranged from 97.38% to 99.32%, with precision (%RSD) below 2%. Sibutramine was detected in 10% of samples (32.1-245.9 µg/g), fluoxetine in 15% (36.6-380.9 µg/g), and both compounds were detected together in 3% of samples. Adulterated unregistered weight-loss supplements were found across all surveyed regions. In conclusion, these findings confirm the presence of undeclared pharmaceutical adulterants in unregistered weight-loss supplements and highlight the need for stronger regulatory oversight, enhanced market monitoring, and greater public awareness to prevent the sale of unregistered products and reduce the associated health risks.

Keywords: Sibutramine, Fluoxetine, weight-loss supplements, adulteration, public health

1. Introduction

The World Health Organization (WHO) defines overweight or obesity as a condition in which there is an abnormally high amount of body fat, which is harmful to health. These conditions were assessed using body mass index (BMI), where a BMI greater than 25 kg/m² is classified as overweight and a BMI greater than 30 kg/m² as obese. Obesity is recognized as a chronic metabolic disease and has become a major global public health challenge. In 2022, WHO reported that approximately 2.5 billion adults were overweight, with more than 890 million classified as obese, representing 43% of the global adult population (World Health Organization, 2025). This substantial and ongoing burden highlights the persistent nature of obesity as a global health challenge, a concern that has been further reaffirmed by the World Obesity Federation (2026). As a result, the use of weight-loss supplements containing natural extracts has increased substantially. A lot of consumers assume these products are safe due to their label as natural. However, this misconception has contributed to the widespread availability of unregistered products, often sold through online and in the markets. These products may pose serious health risks, because they are often adulterated with dangerous chemicals, including compounds banned by regulatory agencies, such as WHO and the U.S. Food and Drug Administration (FDA) (Koncz et al., 2021). Common adulterants in natural weight-loss supplements include sibutramine and fluoxetine. Sibutramine, previously prescribed as an anti-obesity drug, was withdrawn from the global market in 2010 due to serious cardiovascular risks and is not permitted for use in dietary supplements (FDA,

2018; Tucker et al., 2018) It acts by increasing neurotransmitter levels (Serotonin and norepinephrine) to suppress appetite but has been associated with adverse effects such as heart failure, hemorrhagic stroke, and ischemic stroke, particularly in patients with pre-existing cardiovascular conditions (Tucker et al., 2018). Fluoxetine, on the other hand, is an antidepressant that should only be used under medical supervision. When illicitly added to supplements, it may cause adverse effects including nausea, headaches, and significant mood alterations (Kryst et al., 2022). The global demand for natural extract-based products for weight management continues to rise alongside the expansion of the herbal and traditional medicine market (Sargin, 2021). These products are widely promoted through online platforms, social media, and print media, often with exaggerated claims of safety and effectiveness (Ghai et al., 2023; Riaz et al., 2023). However, with increasing demand, unregistered products are frequently marketed through illegal online channels, posing significant risks to consumer health. These risks are particularly concerning when such products are adulterated with hazardous chemical substances. Several reports have indicated that weight-loss supplements marketed as natural extracts may contain undeclared and banned compounds. These include anorectic agents (e.g., sibutramine), anxiolytic agents (e.g., benzodiazepines), antidepressants (e.g., fluoxetine), diuretics (e.g., furosemide and bumetanide), and laxatives (e.g., phenolphthalein), as well as other substances such as pseudoephedrine, phenytoin, caffeine, and thyroid hormones (Koncz et al., 2021). Among these, sibutramine and fluoxetine are the most frequently detected adulterants in natural weight-loss supplements (Firozian et al., 2021; Kim et al., 2014) Several analytical methods have been developed for their detection, including high-performance liquid chromatography (HPLC), ultraviolet (UV) spectrophotometry, liquid chromatography–mass spectrometry (LC–MS), and liquid chromatography–tandem mass spectrometry (LC–MS/MS). Among these techniques, HPLC is widely employed due to its high accuracy, precision, and reliable analytical performance (Fatriyah et al., 2025)

Due to their adverse effects and dose-dependent safety profiles, sibutramine and fluoxetine require careful consideration. Sibutramine was previously prescribed at 5-30 mg/day (commonly 10-15 mg/day) but has been withdrawn in many countries for safety reasons. Fluoxetine remains in clinical use at 20-60 mg/day, up to 80 mg/day in specific indications. Illicit adulteration of both drugs in weight-loss products raises concerns about the safety of "natural" slimming supplements (Afkhami-Ardekani &Sedghi, 2005; Moreira et al., 2024). Recently, the consumption of weight-loss products in Lao PDR has increased significantly through online platforms, direct sales, informal importation, and other unregulated channels. Many of these products are promoted with exaggerated claims and are widely available without adequate regulatory control, increasing the risk of undeclared pharmaceutical adulterants. However, scientific evidence on the adulteration of weight-loss supplements in Lao PDR are limited. Laboratory analysis is therefore needed to evaluate their safety and authenticity. Thus, this study aims to determine the presence and quantity of sibutramine and fluoxetine in unregistered Weight-Loss Supplement Products Containing Natural Extracts marketed in Lao PDR. The findings are expected to support manufacturers and regulatory authorities in strengthening product monitoring, protecting consumer health, and raising public awareness of potential risks.

2. Material and Method

2.1. Chemicals and Reagents

All chemicals and reagents used in the experiments were of analytical grade. Acetonitrile (gradient grade for liquid chromatography), sodium dihydrogen phosphate monohydrate, orthophosphoric acid, and phosphoric acid were purchased from Sigma-Aldrich (Merck, Germany). Deionized water was obtained from a Milli-Q water purification system (Merck, Kenilworth, NJ, USA). Sibutramine hydrochloride reference standard was purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany), and fluoxetine hydrochloride (assigned purity 98%) reference standard was purchased from Tokyo Chemical Industry Co., Ltd. (TCI, Japan).

2.2. Standard Preparation

The standards of sibutramine hydrochloride and fluoxetine hydrochloride were accurately weighed (10 mg each) and dissolved together in the mobile phase in a 100 mL volumetric flask to obtain a stock solution of 100 µg/mL. The combined standard solution was further diluted to obtain working standard solutions and stored in a refrigerator until use.

The mobile phase was composed of 0.01M phosphate buffer (pH 2.5) and acetonitrile (55:45, v/v). Acetonitrile was filtered through a 0.2 µm membrane filter and degassed for 30 min. The phosphate buffer was prepared by dissolving 1.38 g of sodium dihydrogen phosphate (molecular weight: 137.99 g/mol) in distilled water and diluting to 1,000 mL. The pH was adjusted to 2.5 using orthophosphoric acid, followed by filtration through a 0.2 µm membrane filter and degassing for 30 min.

2.3. Chromatographic condition

Analyses were performed using an HPLC system equipped with a UV detector (YL Instrument 9300 System, Korea). Chromatographic separation was achieved on an Agilent C18 analytical column (150 mm × 4.6 mm, 5 µm, USA). The mobile phase consisted of acetonitrile and 0.01 M phosphate buffer (pH 2.5) at a ratio of 55:45 (v/v). The flow rate was set at 1.0 mL/min, the column temperature was maintained at 45°C, and the injection volume was 20 µL. Detection was carried out at 224 nm (Table 1).

HPLC-UV detection was selected due to its suitability for compounds exhibiting strong UV absorbance, providing adequate sensitivity and selectivity for the simultaneous determination of sibutramine and fluoxetine in complex supplement matrices. The detection wavelength (224 nm) was selected based on the UV absorption characteristics of both analytes reported in previous studies (Febriani et al., 2024; Kilicarslan et al., 2010; Maya et al., 2000), and was further confirmed in-house by comparing the chromatographic responses of the reference standards, which demonstrated optimal peak detection and signal intensity under the selected conditions.

2.4. Method validation

The HPLC method was validated in accordance with selected ICH Q2(R1) recommendations for the intended purpose of routine screening. Validation included assessment of linearity, limit of detection (LOD), limit of quantification (LOQ), accuracy, precision, and selectivity, while other parameters recommended for full ICH validation were not evaluated (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH], 2005). Linearity was evaluated in the concentration range of 5-100 µg/mL. LOD and LOQ were determined based on signal-to-noise ratios of approximately 3:1 and 10:1, respectively, obtained from serially diluted standard solutions. Accuracy was evaluated by diluting the stock standard solution to obtain three concentration levels representing low, medium, and high concentrations (25; 55 and 85 µg/mL). Each concentration was analyzed in triplicate, and the peak areas were used to calculate percentage recovery (% recovery). Precision was assessed in terms of intra-day and inter-day variability at three concentration levels (20; 40 and 80 µg/mL), using the percent relative standard deviation (% RSD) as the performance indicator. Intra-day precision was determined by three replicate injections at each concentration within a single day, while inter-day precision was evaluated by repeating the procedure over three consecutive days. And selectivity was examined by comparing chromatograms of standard solutions and real samples. Potential interferences at the retention times of sibutramine and fluoxetine were investigated, and no significant co-eluting peaks were observed, confirming method selectivity in complex herbal matrices.

2.5. Sample Preparation

Samples were collected in various dosage forms, including hard capsules, tablets, jelly, and powders (e.g., instant herbal drink powders and instant coffee blended with herbal extracts). Solid samples (tablets and capsules) were homogenized prior to extraction. An accurately weighed portion (3 g) of each sample was extracted with 20 mL of mobile phase. The mixture was vortexed and sonicated for 15 min, followed by centrifugation at 4000 rpm for 20 min using a refrigerated centrifuge (Sigma Laborzentrifugen GmbH, Osterode am Harz, Germany). The supernatant was collected and filtered through a 0.22 µm membrane filter prior to HPLC analysis.

The 3 g sample mass was selected as a standardized analytical portion to ensure adequate analyte detectability and reproducible extraction across different dosage forms, rather than representing a defined product dosage unit.

3. Result

3.1. Analytical Method Validation

An HPLC-UV method was developed to detect sibutramine and fluoxetine simultaneously in unregistered weight-loss supplements products containing natural extracts. The method exhibited excellent linearity over the concentration range of 5-100 µg/mL, with correlation coefficients (R^2) of 0.9997 for sibutramine and 0.9996 for fluoxetine (Fig. 1). Sensitivity was shown by low limits of detection (LOD: 0.18 µg/mL and 0.19 µg/mL) and limits of quantification (LOQ: 0.55 µg/mL and 0.59 µg/mL) for sibutramine and fluoxetine, respectively.

Accuracy was evaluated using standard solutions due to the absence of matrix-matched recovery experiments, yielding recoveries of 98.06-99.32% for sibutramine and 97.38-99.26% for fluoxetine. Precision, expressed as percent relative standard deviation (%RSD), which indicated good repeatability during the analysis (Table 2). Selectivity was examined by comparing the chromatograms obtained from the standard solutions and sample extracts. The absence of interfering peaks at the retention times of sibutramine and fluoxetine demonstrated that the analytes could be selectively determined under the proposed conditions (Fig. 2).

3.2. Sample Description

The majority of the samples analyzed were products in powder form (52%, n = 52), followed by capsules (32%, n = 32), tablets (13%, n = 13), and jelly (3%, n = 3). Most samples originated from Thailand (92%, n = 92), while smaller proportions were obtained from Vietnam (3%, n = 3), Japan (2%, n = 2), and the Republic of Korea (1%, n = 1). Two samples (2%) had no available information regarding the country of origin. Overall, powder formulations and products sourced from Thailand constituted the majority of the study samples (Table 3). The powder products mainly consisted of instant herbal drink powders and instant coffee products blended with herbal extracts.

3.3. Determination of Sibutramine and Fluoxetine in weight-loss supplement samples

A total of 100 samples were analyzed for the presence of sibutramine and fluoxetine. The samples included various dosage forms, namely capsules, tablets, jelly, and powder products, and were primarily obtained from Thailand, with smaller numbers from Vietnam, Japan, and Korea. Sibutramine was detected in 10 of 100 samples (10%), while fluoxetine was detected in 15 samples (15%). Both sibutramine and fluoxetine were simultaneously detected in three samples (3.0%). The remaining samples showed no detectable levels of either substance (Table 4).

Sibutramine was detected in powder, capsule, and tablet dosage forms, with concentrations ranging from 32.1 to 245.9 µg/g. Fluoxetine was primarily detected in powder and capsule forms, with concentrations ranging from 36.6 to 380.9 µg/g. However, due to the lack of information on product unit mass and dosage recommendations, estimation of daily intake (µg/day) was not possible. Notably, three samples (VT7, LP2, and LP9) contained both sibutramine and fluoxetine. Among these, sample LP9 exhibited relatively high concentrations of both sibutramine (138.7 µg/g) and fluoxetine (234.4 µg/g) (Table 5).

The results of this study indicate that undeclared pharmaceutical ingredients were found in some unregistered products, with significant variations in the concentration of active ingredients across different samples and dosage forms. However, adulteration was detected in samples from all surveyed provinces, with the highest proportion observed in Luang Prabang (35%), followed by Vientiane Capital (27.5%) and Champasak (20%), while Savannakhet showed the lowest detection rate (5%).

4. Discussion

An HPLC-UV method was developed and validated in this study for the simultaneous determination of sibutramine and fluoxetine in unregistered weight-loss supplements containing natural extracts. The method showed satisfactory analytical performance, including excellent linearity, low limits of detection and quantification, high recovery (>97%), and good precision, with both intra- and inter-day % RSD values below 2%. These results meet the validation criteria outlined in the ICH Q2 (R1) guideline, indicating that the method is reliable and suitable for routine screening and quality control applications. Accuracy was assessed using standard solutions, and matrix recovery of the spike substances was not analyzed in the experiments due to the complexity of matrices in herbal supplements and the variety of dosage forms. Matrix effects and extraction efficiency may affect analytical performance, including potential signal reduction or enhancement. Previous studies have reported that complex herbal matrices can significantly affect analytical performance due to co-extracted interferences, highlighting the importance of matrix-based validation (Wei et al., 2026; Zhang et al., 2023). However, this method demonstrated good selectivity when applied to real samples, with no significant interfering peaks observed at the retention times of sibutramine and fluoxetine. Similar approaches have been reported for screening pharmaceutical adulterants in herbal supplements, where selectivity is a critical parameter for reliable detection (Azab et al., 2022) These findings are consistent with previous studies emphasizing robust chromatographic performance, including high linearity and sensitivity, for the accurate determination of adulterants in complex matrices (Nguyen et al., 2024). Chromatography methods, particularly HPLC, remain widely used for the detection of undeclared pharmaceutical products due to their high separation efficiency and ability to analyse multiple substances simultaneously. In addition, HPLC can be coupled with various detectors, such as UV, diode array detector (DAD), and fluorescence detector (FLD), to enhance analytical performance (Ariburnu et al., 2012; Pratiwi et al., 2021; Zhivikj et al., 2020).

Among the analyzed products, powders represented the most common dosage form (52%), followed by capsules (32%), tablets (13%), and jelly (3%). Powder products mainly consisted of instant herbal drinks and coffee-based formulations, which are commonly marketed as convenient weight-management products. This finding is consistent with previous reports indicating that products labelled "natural" or "herbal" are often produced in powder or beverage form because these formats are easier for consumers to accept and reduce the likelihood of adulteration (Krivohlavek et al., 2016; Reeuwijk et al., 2014). The majority of the samples originated from Thailand (92%), reflecting the distribution pattern of unregistered products available in the study setting and suggesting substantial cross-border circulation of such products.

Analysis of 100 samples revealed that sibutramine was detected in 10% of samples, fluoxetine in 15%, and both were detected simultaneously in 3% of samples, representing a total of 22 adulterated samples. This detection rate is comparable to the results of surveillance studies in other regions, in which sibutramine has consistently been reported as one of the most frequently detected adulterants in weight-loss supplements (Phan et al., 2025). For example, a survey conducted in the United Arab Emirates identified undeclared sibutramine in approximately 15% of samples and fluoxetine in 5%, with an overall adulteration rate of 17.5% (Jairoun et al., 2021). Similarly, studies conducted in Korea and Europe have reported sibutramine as a major adulterant, often accompanied by other pharmaceutical substances, including fluoxetine (Gheorghiu et al., 2025; Kim et al., 2014)

Quantitative analysis of adulterated samples revealed considerable variability in the concentrations of sibutramine (32.1-245.9 μg/g) and fluoxetine (36.6-380.9 μg/g). Such variability has also been reported in previous studies and may expose consumers to unpredictable effects, ranging from subtherapeutic to potentially harmful doses. Notably, three samples contained both sibutramine and fluoxetine, which may increase the risk of adverse cardiovascular and neuropsychiatric effects due to potential combined or interacting pharmacological actions (Hachem et al., 2016; Scheen, 2011)

Geographically, adulterated samples were identified in all surveyed provinces, with the highest proportion observed in Luang Prabang, followed by Vientiane Capital and Champasak, while Savannakhet showed the lowest detection rate. These studies indicate that adulterated products are widely distributed across regions, possibly reflecting differences in supply chains, product sources, and local market conditions. Compared to result from other regions, the adulteration rates found in this study (10-15% for each substance) appear slightly lower, but still represent a significant public health problem. The differences among provinces may be related to variations in regulatory activities, product distribution channels and the extent of market surveillance. Despite these differences, the detection of undeclared pharmaceutical ingredients confirms the potential risk associated with products marketed as "natural" weight-loss supplements. These findings emphasize the importance of continuous regulatory monitoring, routine product testing, and improved consumer awareness to reduce exposure to adulterated products.

5. Conclusion

This study demonstrated that a proportion of unregistered weight-loss supplement products in Lao PDR are adulterated with undeclared pharmaceutical substances, specifically sibutramine and fluoxetine. These research findings highlight potential public health concerns for the local population, particularly unsuspecting consumers. The presence of multiple contaminants simultaneously in certain products increases the risk of adverse health effects. Due to the variation in detected concentrations and the lack of dosage information, the potential exposure and associated risks remain uncertain but warrant concern. These results provide important evidence for strengthening regulatory enforcement and routine market surveillance in Lao PDR and may also be relevant to regional public health monitoring in similar settings. Therefore, regular inspections and the implementation of quality control measures are crucial steps in improving the safety of unregistered weight-loss

supplements. Combined with increased public awareness and the establishment of a systematic system for monitoring side effects, these measures can help reduce the potential risks associated with using these products.

6. Conflicts of interest

The authors declare that they have no conflicts of interest.

7. Acknowledgments

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Table 1. Detailed chromatographic conditions

	Sibutramine	Fluoxetine
Wevelength (nm)	224	224
Flow rate (1mL/min)	1.0	1.0
Injection volume (µl)	20	20
Mobile phase	Phosphate buffer 0.01M pH 2.5: Acetonitrile (55:45)	Phosphate buffer 0.01M pH 2.5: Acetonitrile (55:45)
Column	Agilent C-18 5μm4.6 mm x 150	Agilent C-18 5μm4.6 mm x 150
Temperature	45°C	45°C
Retention Time	3.8 minutes	3 minutes

Table 2. Accuracy (mean recovery, %) and precision (% RSD) of sibutramine and fluoxetine

Substance	Recovery (%) (n=3)			Precision	
	25 µg/ml	55 µg/ml	85 µg/ml	Intra-day % RSD (n=9)	Inter-day % RSD (n=27)
Sibutramine	98.06±0.66	99.21±0.88	99.32±042	0.42	0.93
Fluoxetine	97.38±0.53	98.89±0.52	99.26±0.50	0.44	1.13

Table 3. Distribution of characteristics of analyzed samples (n = 100)

Variable	Category	Frequency	Percentage
Dosage form	Powder	52	52%
	Capsule	32	32%
	Tablet	13	13%
	Jelly	3	3%
Country of origin	Thailand	92	92%
	Vietnam	3	3%
	Japan	2	2%
	Korea	1	1%
	NA*	2	2%

Table 4. Percentage of Adulterated Substances in weight-loss supplements containing natural extract products (n = 100)

No.	Adulteration Substance	Number of Samples Detected	Percentage (%)
1	Sibutramine	10	10
2	Fluoxetine	15	15
3	Sibutramine & Fluoxetine	3	3

able 5. Quantification of sibutramine and fluoxetine in adulterated samples

No.	Code	Country of origin	Dosage Form	Sibutramine content (µg/g)	Fluoxetine content (µg/g)
1	VT1	Thailand	Powder	-	206.8
2	VT3	Thailand	Capsule	39.7	-
3	VT7	Thailand	Capsule	44.2	71.4
4	VT17	Thailand	Powder	-	189.5
5	VT19	NA	Powder	-	376.6
6	VT23	Thailand	Tablet	68.5	-
7	VT27	Thailand	Tablet	61.2	-
8	VT31	Thailand	Tablet	43.2	-
9	VT33	Thailand	Capsule	-	125.6
10	VT40	Thailand	Capsule	-	110.1
11	LP1	Thailand	Powder	245.9	-
12	LP2	Thailand	Powder	32.1	36.6
13	LP5	Thailand	Powder	-	133.9
14	LP8	Thailand	Capsule	38.3	-
15	LP9	Thailand	Capsule	138.7	234.4
16	LP10	Thailand	Powder	-	36.9
17	LP13	Japan	Tablet	178.7	-
18	SV8	Thailand	Powder	-	380.90

19	CP3	Thailand	Capsule	-	361.71
20	CP12	Thailand	Powder	-	187.0
21	CP13	Thailand	Powder	-	350.6
22	CP18	Thailand	Powder	-	174.8

Note : Sample codes indicate collection locations (VT: Vientiane Capital ; LP: Luang Prabang; SV: Savannakhet ; CP: Champasak). Only samples with detected adulterants are presented in this table; NA: Not available.

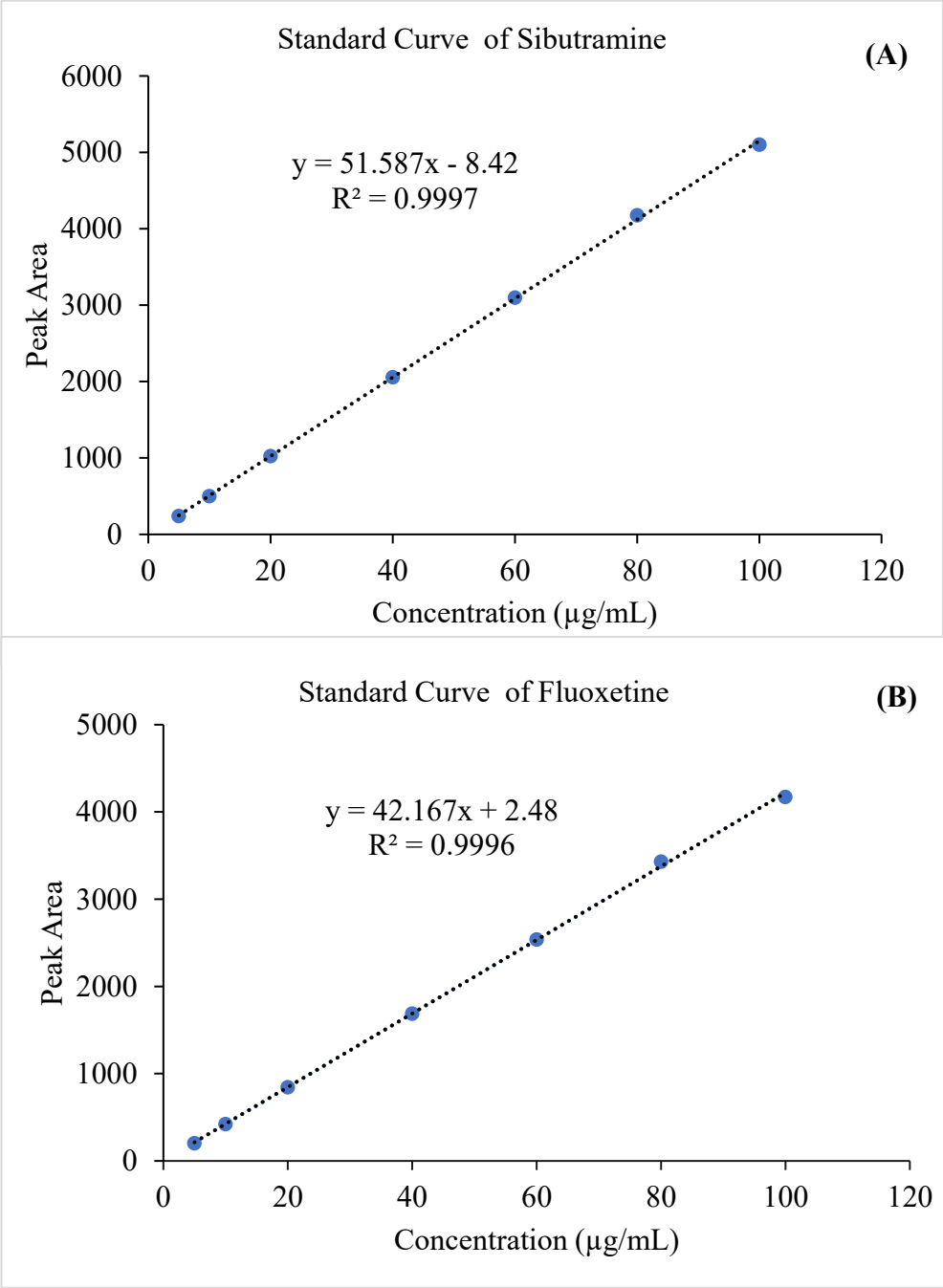

Figure 1. Standard calibration curves of Sibutramine (A) and Fluoxetine (B).

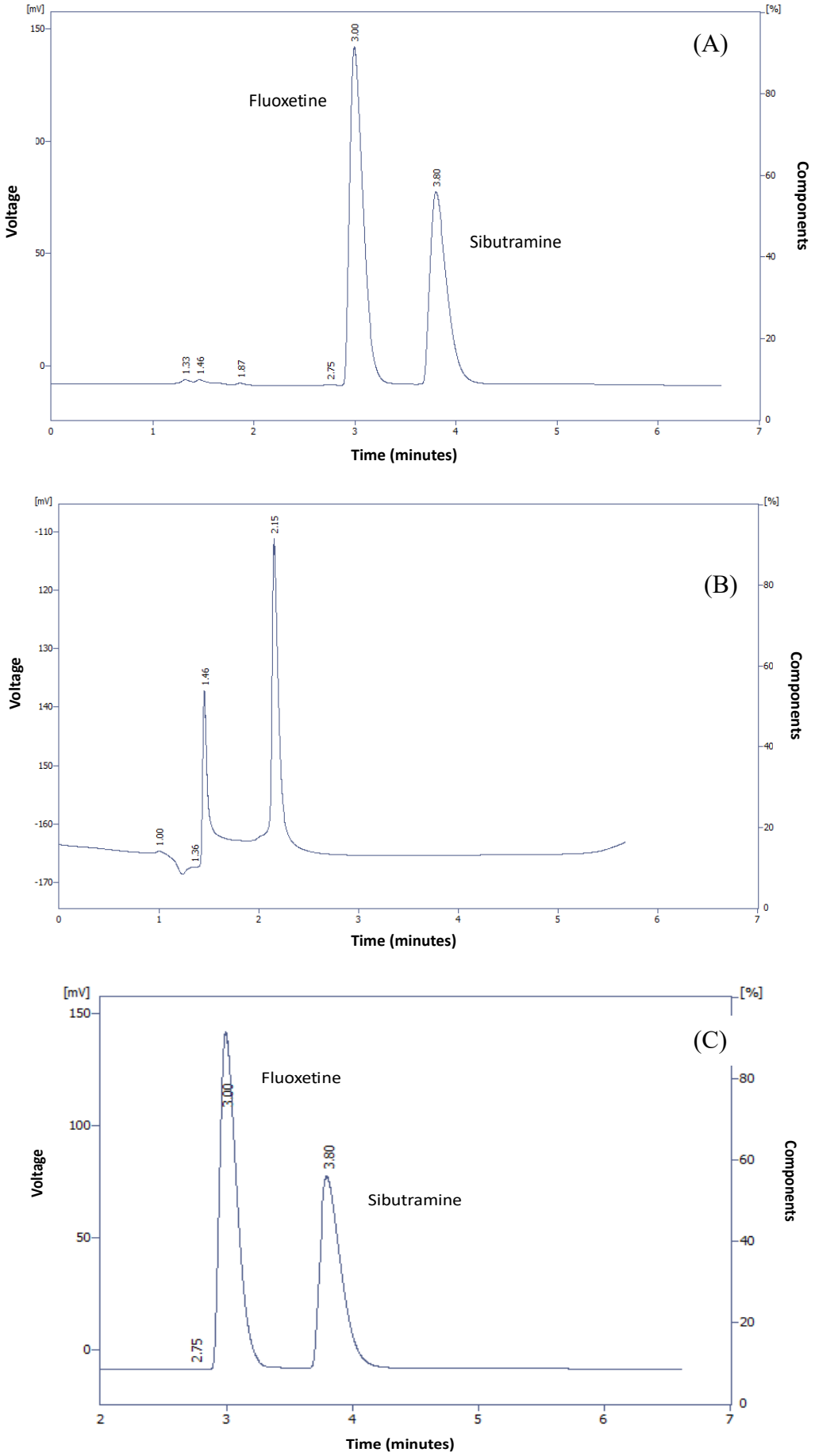

Figure 2. HPLC chromatograms of sibutramine-fluoxetine standard mixture (A), blank (B), and sample (C).